THE PROBLEM

OF

PULMONARY TUBERCULOSIS

CONSIDERED FROM

THE STANDPOINT OF INFECTION

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The history of tuberculosis is that of many other diseases. In point of time comes, firstly, the accurate symptomatological concept, and, secondly, the attempt to determine the real essence of the disease by the aid of pathological anatomy. The experimental period follows in quick succession, and lastly in our own day, the discovery of the actual cause constitutes what one may legitimately call the ætiological era. When the medical student of modern days is taught that tuberculosis is a specific infective malady caused by the bacillus of Koch, he is apt to think that the whole problem is solved in this simple expression. A study of the facts shows that in reality the problem is much more complicated, and in his enthusiasm for the new teaching he is apt to discard other factors in the case, factors which, prior to the ætiological era, were apparently well established, or indeed were regarded as fundamental. Before dealing with the concrete subject of this lecture I should like to refer briefly to the ideas which had accumulated prior to the epoch-making discoveries of M. Villemin in 1865. The knowledge of tuberculosis which has come down to us from past ages in the *Corpus Hippocraticum*, in the writings of the Roman Encyclopædists, in Areteios and in Claudius Galenus, show that the main clinical features of the disease as witnessed in the lungs were already well known. Indeed Hippocrates had given an account of the φύματα or circumscribed inflammatory foci which soften and lead to the formation of caverns. Nothing of cardinal importance was added to his account until after the revival of learning. The foundations of anatomy, normal and morbid, were being laid, and a more complete knowledge of the structure of the tuberculous lesions became possible. Sylvius therefore soon recognised that the essence of the disease is to be sought in the anatomically recognisable *tubercles*, although their exact origin was to him, as to many of his successors, a puzzle. Unfortunately, the view that he felt himself justified in taking, hampered advance for more than a hundred years. As is well known, he derived tubercles from the degeneration of small invisible glands seated in the substance of the lung, and he considered that the tuberculous change was analogous to the

scrofulous change so common in the glands of the neck and mesentery. In his learned Phthisiologia (1694), Richard Morton, Surgeon of Newgate Street, could come to no other conclusion. "Crude tubercle" he says "is bred from the obstruction of some glandular part of the lungs, to wit, when a great quantity of serum or water is separated from the blood than is thrown out by the duct of the glandule, from whence it comes to pass that the part affected, being too much distended by the humour that is imprisoned in it, is deprived of natural tone and thereupon is no longer able to spend or throw out the serum or water which flows into it or is separated, so likewise the humour that is so shut up not being more renewed by an influx of fresh humour does by degrees grow dry and hard from the natural heat of the part from whence arises a hardness that resists a pressure or a tubercle of which we are now speaking, which in progress of time is wont to be inflamed and to turn to an apostem sooner or later" (p. 82). Forty years later, these views were destined to undergo a serious modification at the hands of Pierre Dessault, a Physician of Bordeaux, who for many years had made an extensive study of the disease and had acquired great intimacy with its pathological-anatomical features. From him may be said to have started our modern conceptions of the histogenesis of the tubercle, although much that he discovered was neglected and forgotten, and was re-discovered by William Stark, a young Physician of St. George's Hospital, whose untimely death at the age of 29, brought about by experiments on his own body, robbed English pathology of one of its earliest and most accurate observers. Dessault was unable to accept the glandular origin of tubercles but alleged that they originated in the body as new structures. Stark went further and was able to reconstruct the evolution of the tubercle and its relation to phthisis in all its essential peculiarities. He pointed out the variability in the size of tubercles, their solidity, their absence of vessels, their tendency to colliquation, their gradual confluence and their relation to caverns. The sites of cavity formation, the hepatisation of the lungs, the obliteration of the vessels, the thickening of the bronchi, the ulceration of the intestine, all attracted his attention and were carefully described. Indeed, as far as macroscopic appearances are concerned he left little for subsequent enquirers to add. Even prior to the publication of Stark's work which was made in 1788, eighteen years after his death, his observations would appear to have been known, for they are referred to by Reid in 1782, and a complete confirmation was made by Matthew Baillie, of St. George's Hospital, in 1793. From Stark and Baillie dates what one might call the modern era of tuberculosis, an era corresponding roughly in point of time with the nineteenth century, and divisible into four great periods. Each of these periods presents identical characteristics. The period is inaugurated by the advance of some particular investigator, an advance not capable at once of substantiation, but in the end proving to be

correct. Subsequent to the advance we have intensive researches on the part of imitators of the original, some affirming, some denying the new conclusions. In the course of time, often of years, we see the passage into more tranquil waters and the acceptation of the new knowledge which becomes transmitted as an authoritative canon. If I may anticipate what I shall say later, I hasten to add that the periods I allude to are those associated with the names of Laennec, Villemin and Robert Koch.

In France the new doctrines of Stark and Matthew Baillie were taken up by Portal, although perhaps not in their entirety, and it was mainly through him that great confusion was wrought as to what is tubercle and what is not. This resulted from the fact that he used the term tuberculosis in a much wider sense to include what had previously been called scrofula. The term had been used only for the condition in which there are definite "tubercles," whereas he now introduced into the question pathological changes which *resemble* those found in tubercles. From the time of Portal dates the long history of the relations existing between scrofula and tubercle. By the beginning of the nineteenth century the subject was already one of burning interest, and the concept of tuberculosis and phthisis had become wider and wider. To this period belongs the work of Bayle (1774–1816), whose observations led him to conclude that phthisis is a general name for a number of different conditions which he classified as tuberculous, granular, melanotic, ulcerative, calculous and cancerous. It is to Bayle that we largely owe the idea of a tuberculous diathesis, an idea destined to play such an important part in all subsequent discussions on the subject. The evolution of this diathetic idea is to be found in the observation of tubercle not only in the lungs but in many other parts of the body, showing, apparently, that the condition is not only local but general. There is, as Bayle expressed it, a "*tendance à la production des tubercules ou diathèse tuberculeuse qui est la cause la plus ordinaire de la phthisie pulmonaire.*"

The common cause of phthisis is a tuberculous degeneration which is essentially a chronic malady and a form of scrofula. It was at this moment that Laennec took up the subject, and, with the intuition of a genius superadded to consummate powers of observation, he asserted the belief of the unity of phthisis. When one considers the difficulties of the subject and the defective and undeveloped methods of investigation which he was compelled to employ, Laennec's work must always rank with the greatest advances in medicine. His deductions indeed were so far ahead of the time that it was only long years after his death, and when the storm they had raised had calmed down, that their full import became recognised. He affirmed that the tuberculous process is a definite pathological change irrespective of its site, and it is seen in two forms, nodules or tubercles, and diffuse tuberculous infiltration.

The tuberculous infiltration is amorphous, grey or yellow. All are of one origin—the miliary nodule. The new doctrines created a sensation. From all quarters streamed the publications of the views or the observations of others. The history of the period would fill a book. I can only name the principal partizans but to refresh your memories. In France, Broussais, Gendrin, Andral, and particularly Louis; in England, Barron, Carswell, James Clarke. In this country the work of the two latter was largely accepted as final, and was widely disseminated through the medium of Sir Thomas Watson's "Principles and Practice of Physic." In Germany, Schönlein and Canstatt; in Austria, Rokitansky upheld the new doctrines. By this time the microscope had become a necessary instrument in medical research. The essence of tubercle was probably to be found by its aid, and already in 1849 Lebert was in the field searching for and finding his "tubercle corpuscle." In Germany, Virchow and Henle attacked the doctrine of Lebert, and this led to a prolonged investigation by Virchow, his work bringing this period more or less to a definite close. It is impossible to analyse Virchow's work in detail. Its main trend can only be referred to briefly. It is essential, he said, to separate the miliary tubercle from Laennec's tuberculous infiltration. Caseation is not pathognomonic for, or synonymous with, tubercle. The essence of tuberculosis is to be sought in the young cellular mass—the tubercle—which he described as "a pitiful production, a new formation, from its outset miserable and destined to degeneration and decay." The caseous transformation is the regular termination of tubercle, but it is not the necessary one. The term "tubercle," he considered, should be reserved for the miliary granulation; that which Portal, Bayle and Laennec called tuberculous is, according to Virchow, not specific. He called it caseous, and regarded the condition as the result of a diathesis—a manifestation of tissue vulnerability. "No one," he says, "has, up to the present, produced experimental tuberculosis." Virchow's work was confirmed and developed by Rindfleisch, Ernst Wagner, Schüppel, Langhans, Friedländer, Baumgarten, Arnold and Weigert, and constitutes the current pathological-anatomical doctrines of to-day. Thus ends the first great period of anatomical research. Its conclusions are incomplete. The difficulties are such that the essence of the process cannot be solved by the ordinary methods of histology.

In 1857 Buhl introduced into the whole subject a new idea which became the germ of the second period associated with the name of Villemin. Buhl emphasised the constant dependence of miliary tuberculosis on a pre-existing caseous production, and correctly interpreted the relation of the two as that of cause and effect. Tubercle, according to him, is a specific resorptive or infective disease originating in the absorption of a special poison into the blood. The relation of a primary caseous focus to a subsequent

miliary tuberculosis was confirmed by Ponfick, and in a particularly clear manner by Weigert, Benda and Schmorl in more modern times. The work of Buhl brings us into contact with the period of experimental research—a period inaugurated by the communication of Villemin's work, by Claude Bernard, to the Academy of Sciences, séance du 4 December, 1865. The communication bore the title "Cause et nature de la tuberculose." * In his paper Villemin shows himself to be an investigator of the first rank, not only in regard to the way his experiments were planned and carried out, but in the deductions which were legitimately to be derived from them.

In his earlier experiments he inoculated tuberculous matter, mostly on several occasions, into small wounds made behind the ears. After some weeks the animals were killed and found to be tuberculous to a greater or less extent. Control uninoculated animals kept under precisely similar conditions remained well. Animals inoculated with material other than tuberculous did not contract tuberculosis. The experimental lesions produced by tuberculous matter are identical with those found in the disease contracted under natural conditions. Already in his first publication he was able to conclude that tubercle is a specific disease, its cause resides in an inoculable agent. Tuberculosis belongs to the category of virulent diseases, and in the nosological system is to be placed in alliance with diseases like glanders and syphilis. In another publication he contributed fresh experimental data, , and finally published his complete researches under the title "Etudes sur la tuberculose; preuves rationelles et expérimentales, de sa specificité et de son inoculabilité," Paris, 1868. In this book there is much experimental work dealing with the transmission of tuberculosis from man to animals, and from cattle to animals. Of particular interest are his observations (p. 538) on the inoculability of tuberculous material from *man* into rabbits. "We must remark," he says, "that none of our rabbits inoculated with human tubercle have presented a tuberculisation so rapid and generalised as that which we have obtained with material from the cow. At first we were inclined to regard this as fortuitous, but subsequent experiments led us to suppose that the tubercle of the bovine race inoculated into rabbits possesses a much greater activity than that obtained from man. It may be supposed that, like all virulent matter, the tuberculous matter is the more virulent the more the affinity of the animal supplying the virus and the animal receiving it."

In his conclusions, Villemin discusses in a masterly and advanced way the whole problem of tuberculosis, and emphasises the conclusion

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* *Note.*—Villemin was born at Prey in 1827, and studied in Strassburg. Entering the medical department of the French army in 1848, he rose to the rank of professor agrégé at the Val-de-Grace, retiring with the rank of Inspector General. He died in 1892.

he had reached that the body does not produce the virus. The virus is not the lesion but causes the lesion. In the prophylaxis of tuberculosis two points are of cardinal importance, viz. (1) the knowledge of the existence and condensation of the morbid ferment; (2) the "aptitude du milieu organique." In any attempt to stamp out tuberculosis, hygienists must consider both these factors. Villemin's last publication (1869) is concerned particularly with the propagation of pulmonary phthisis, and contains ingenious and fundamental experiments on the infectivity of sputum under varying conditions, observations on the factors determining consumption and a scheme for its prevention. It was about this time (1867) that William Budd, of North Tawton, had arrived independently at similar conclusions, based particularly on the geographical distribution of consumption in past and present times, and especially its great fatality now, in countries which, when first discovered by Europeans, were known to be entirely free from it. He inferred that tuberculosis is a true zymotic disease of specific nature in the same sense as enteric fever. It never originates spontaneously, but is perpetuated solely by the law of continuous succession. "The tuberculous matter itself," he says, "is (or includes) the specific morbid matter of the disease, and constitutes the material by which phthisis is propagated from one person to another and disseminated throughout society."

From the epoch-making work of Villemin and Budd, especially the former, dates the separation of tuberculosis into two fundamental problems, the virus on the one hand, and the *milieu organique*, *terrain* or soil on the other. Although experimenters prior to Villemin (see Boisseau Quelques mots sur l'inoculation du tubercule au point de vue historique, L'Union méd, Paris, 1868, 3s., Vol. V., p. 15), had made attempts to transmit tuberculosis experimentally, his was the first carried out systematically on an extended scale. His conclusions were revolutionary, and immediately created a great sensation, proving heuristic in the highest degree for the whole question of tuberculosis. On all sides experimental work was set afoot, and as the results streamed into the medical publications of the period, it was at once apparent that unanimity of opinion had not been reached. In particular, experimentalists differed on the fundamental question whether experimental tuberculosis is produced only from the inoculation of tuberculous matter, or whether it may also occur after the introduction of matter not known or suspected to be tuberculous. The latter view was the one taken by Lebert and Wyss, Cohnheim and B. Fränkel (at first), Waldenburg, Simon, Burdon-Sanderson and Wilson Fox. Sir Andrew Clarke also adopted their view in his Croonian lectures in 1867. At first then, the balance of opinion was against Villemin's theses. In Germany, however, the work of Edwin Klebs (1868), and later of Cohnheim, turned the scale in Villemin's favour, although discussion on the

subject continued with great zest for a number of years, ending ultimately, however, in the complete acceptation of the new doctrine.

Even from the date of Villemin's first publication, the importance of the relationship of human to bovine tuberculosis was clearly discernible. As we have seen, he appeared to consider that they were not identical, at any rate in their experimental types. But as the matter was of prime importance, from a hygienic point of view, it soon became one of intense study. As a result of experiments, carried out by Gerlach, Günther and Harms, Rivolta and Perroncito, Zurn, and particularly Bollinger and Toussaint, it was soon accepted that bovine tuberculosis is communicable to experimental animals by inoculation and by ingestion. Even at this time, however, the experiments of Bollinger, Orth and others showed that when human tuberculous matter is fed to animals, especially rabbits, negative results usually follow. The animals do not contract tuberculosis. The foundations of the belief that tuberculosis in man and cattle is due to one and the same virus are not easy to trace historically. Parallels are found in all branches of medicine. An idea becomes current, its source is indefinite. In time, however, the idea becomes fixed; some inquirer seeks its true source, only to find that it is uncertain or nebulous, and by degrees it vanishes, or its importance becomes properly evaluated. It is like the rivers which travellers tell us exist in the Asiatic deserts. They begin as rills in the sand, become confluent to streams, then to rivers of magnitude, coursing, perhaps, for hundreds of miles, to end imperceptibly again in the lone and level sands from which they took their birth. So far as I have able to learn, from an enquiry into the literature of the period in question, Klebs (*Zur Geschichte der Tuberculosis*, *Virchows Archiv*, 1870, Bd. xliv., p. 291) was the first definitely to assert that *perlsucht* of cattle owes its origin to the same virus as that of human tuberculosis. Guinea pigs, fed with *perlsucht* matter, yield lesions identical with those in similar animals fed with human tuberculous matter. One experiment is quoted in which a calf was inoculated with human tuberculous matter. Of the latter, 15 Pravaz syringefuls (l) were inoculated into the peritoneal cavity of a beautiful young calf, four weeks old, and the autopsy revealed a large number of pearl nodules and miliary tubercules in the mesentery, a few nodules in the liver, one or two in the spleen, none in the lungs, kidney or intestines. The germ thus sown by Klebs took root, and it soon became an accepted fact that human and bovine tubercle owe their origin to an identical virus. Klebs' views, advanced as they were, came at a time when the problem raised by Villemin had not been definitely accepted. This acceptation was largely due to the classical experiments of Cohnheim and Salomonsen (1878) on the result of transferring tuberculous and non-tuberculous matter into the anterior chamber of the eye of animals. The specificity of tubercle was proved. The identity of bovine and

human tubercle was not completed. On looking through the experimental work on intra-ocular inoculation, it is to be observed that in many instances, where bovine material was transplanted to the anterior chamber of the rabbit, the result was a generalised tuberculosis, in addition to a destruction of the bulbus, whereas with human material the result was frequently entirely local, or, at most, involved the regional glands. The recent experiments of Oehlecker confirm this entirely. The deadly results produced by causing guinea pigs to inhale tuberculous sputum could not be denied: feeding experiments were less convincing, especially where the tuberculous material was human and the experimental animal the rabbit or the calf. Johne, himself a supporter of the doctrine of the unity of human and bovine tuberculosis, summed up a critical inquiry into the published work by the assertion that positive results with human material were relatively more difficult to obtain. The second great tuberculous era of the nineteenth century thus comes to an end with the beginning of the eighth decade. Its termination is marked by the universal acceptation of Villemin's principal thesis: tuberculosis is inoculable; tuberculosis is a specific disease.

The last great epoch opens with the communication of Robert Koch, "Ueber Tuberculose," on March 24th, 1882, in the Berlin Physiological Society, his complete research, "Die Aetiologie der Tuberculose," which appeared two years later, being at once accepted as one of the greatest achievements in medical science. In it we have the isolation of the actual virus of tuberculosis, the bacillus tuberculosis, and the demonstration of the unity of tubercle as a pathological process—a complete and irrefutable confirmation of the doctrines of Laennec and Villemin. Little has been added to the pure bacteriology of tubercle since Koch's paper, which shows his greatest characteristics, even at this early period of his career, superb technique, unerring accuracy and calm and dispassionate logic which prevented him drawing conclusions beyond the reach of the facts which he so clearly proved. From all sides his work was at once completely confirmed and passed into medical teaching as a dogma. Subsequent years were taken up with working out details. With regard to the question of bovine and human tubercle, Koch expressed himself as convinced of their essential identity. From a hygienic point of view the same precautions must be adopted against *perlsucht* bacilli as against infection by tubercle bacilli, until it is proved that in the human being perlsucht bacilli may, with safety, be brought into contact with wounds of the skin without giving rise to tuberculosis. So far as I can find, Koch did not inoculate any bovine animals with human tuberculous matter at this period, but he emphasised the great importance of the dissemination of sputum as the principle vehicle carrying the virus of tuberculosis. Like Villemin he considered that pulmonary phthisis, the commonest form of

tuberculosis, is essentially an inhalation disease communicated from the dried sputum of consumptives.

Between 1882 and 1900, very few seriously doubted that bovine and human tubercle were identical. Hygienists, indeed, were in the front rank passing stringent regulations at their various congresses, with regard to the danger of tuberculous bovine material, meat or milk. Dissentient voices, however, were raised here and there—in this country by Sidney Martin, in America by Frothingham, Dinwiddie, and in particular by Theobald Smith, 1898. This culminated in the historic utterances of Koch himself, at the British Congress of Tuberculosis in 1901. He referred to his older views and added that proved facts which would have enabled him sharply to distinguish bovine from human tuberculosis were not then at his disposal. He now referred to experiments undertaken in collaboration with Schütz which led him to the belief that the two diseases are not identical. A number of young cattle which had stood the tuberculin test were infected in various ways with pure cultures of bacilli of human origin, or sputum was injected under the skin, into the peritoneal cavity or jugular vein. Others were fed with tuberculous material or inhaled it. Of 19 animals used in the experiments none showed clinical evidences of tuberculosis, and when slaughtered at the end of 6–8 months no tuberculosis could be found in their internal organs. It was only at the places where the injections had been made that small suppurative foci had formed, in which a few tubercle bacilli could be found.

When, on the contrary, similar experiments were made with tuberculous matter of bovine source, the severest tuberculous disorders broke out in all the infected animals, and to the accompaniment of high fever and emaciation, death set in with far advanced tuberculosis, especially of the lungs and spleen. "Considering these facts," Koch said, "I feel justified in maintaining that human tuberculosis differs from bovine, and cannot be transmitted to cattle." With regard to the question of the infectivity of man from bovine material, this does not lend itself to experimentation, but from various pathological considerations he asserted it was unlikely. "I therefore do not deem it advisable to take any measures against it. Though the important question whether man is susceptible to bovine tuberculosis at all is not yet absolutely decided, and will not admit of absolute decision to-day or to-morrow, one is, nevertheless, at liberty to say that if such a susceptibility exists, the infection of human beings is but a rare occurrence. . . . . The only *main* source of the infection of tuberculosis is the sputum of consumptive patients, and the measures for the combating of tuberculosis must aim at the prevention of the dangers arising from its diffusion."

Koch's London address created an immense sensation, and was followed by renewed research all over the world. In particular, Commissions were appointed, especially in Germany, England,

Sweden and elsewhere, and, in addition, private investigators, notably Theobald Smith, Arloing, Fibiger and Jensen, Beitzke, W. H. Park, Kitasato, have made material advances. While the tuberculosis commissions were getting to work, the medical world was again shaken by the categoric statements of von Behring in his address at Kassel, in 1903. According to him, milk is the main source of phthisis, " Die Säuglingsmilch ist die Hauptquelle für die Schwindsuchtsentstehung." These views of Koch and Behring have led to a thorough investigation of the whole problem of the origin of human tuberculosis and its relation to bovine tuberculosis, and it is mainly with the latter relation that I wish to deal. The principal problems for which a solution has been sought are :— (1) What is the main source of pulmonary tuberculosis, the commonest of all forms of tubercle ? Do the bacilli enter the body by the respiratory system or the digestive system ; in other words, is the infection in pulmonary tubercle ærogenic or enterogenic ? (2) Are the bacilli found in consumption of human or bovine type ? With regard to the frequence with which human beings are attacked with tuberculosis there is more or less unanimity.

From the researches on hospital autopsy material, Naegeli, Burkhardt, and Harbitz consider that about 90% or more of all cadavera show tuberculous lesions, lethal, active latent, inactive latent or healed. Lubarsch places the percentage lower, viz., 69·1 % in people over 16 years of age. Necker has recently tried to explain these differences, and concluded from his own observations in Vienna, that the higher figures of Naegeli and Burkhardt are due to the inclusion of lesions suspected to be but not proved to be tuberculous. His results showed 70·21% of cases certainly tuberculous, and 92·55% where suspected or doubtful cases were included. It is, of course, a question how far hospital autopsy material is immediately applicable to mankind in general, as hospital material is of a special kind. Nevertheless, it cannot be doubted that a very large number of people in adult life reveal tuberculous lesions *post mortem*.

With regard to children below 15 years opinions differ, some holding that the frequence of tubercle increases progressively, others that it is interrupted at certain ages (Sehlbach). With regard to the origin of tuberculosis in general it must be admitted that in most civilised countries the conditions are so complicated that in spite of elaborate researches by Newsholme and others it has not been possible to obtain clearness. Other methods must be adopted, and it may at once be said that these are of three types—(1) pathological anatomical methods; (2) epidemiological studies, particularly in countries in which the conditions are for some reason or other relatively simple; (3) study of cultures of tubercle bacilli isolated from cases of pulmonary or other forms of tuberculosis.

I. With regard to the first of these, viz., the paths of infection in pulmonary tuberculosis, I have made a fairly complete analysis

in my artiele in "Clifford-Allbutt-Rolleston's System of Medicine" (1909. Vol. V., p. 299). It is unneccssary to repeat the details here. The conclusion which I formed after carefully studying the whole question, was that the principal or almost exclusive source of pulmonary tuberculosis is the inhalation of bacilli from sputum, which is the old view held by Villemin and Koch, the arguments in favour of this being the great dissemination of sputum from multitudes of consumptives, the early anatomical lesions in the lungs, and the fact, widely confirmed, that doses of tubercle bacilli which, when inhaled, cause pulmonary tuberculosis, produce no effect when ingested. The attempt by Calmette Vansteenberghe and Grysez to prove that pneumoconioses, like anthracosis, and tuberculosis, are caused by infection from the alimentary system and not aerogenically, has, with scarcely an exeeption, met with universal contradiction of workers in different countries, and most recently by Cobbett in this country. While, therefore, the balance of opinion is in favour of aerogenie infection, it must perhaps be admitted that the problem is not capable of solution by pathologieal-anatomical methods.

II. Epidemiological data. Since the question of human and bovine tuberculosis has again been acutely raised, a number of investigations of an epidemiological character have been undertaken. These have concerned, in part, cases in which tuberculosis of bovine type have occurred in people whose occupations bring them into contact with animals or animal products. Cases of these kind, besides being rare, are also difficult correctly to interpret, and therefore, to a certain extent, untrustworthy. In part, data have been collected with regard to the history of people known to have consumed tuberculous milk over long periods. Recent studies carried out by Weber for the Kaiserliche Gesundheitsamte point to the conclusion that such people do not become affected with tubercle more frequently than others not thus exposed. In Weber's series, 360 people, including 151 children, were known to have drunk unboiled milk of tuberculous cows, or consumed butter, buttermilk or cheese made with such milk over some period. In spite of this fact, an infection with perlsucht bacilli could only be determined in two cases, both children, and both with cervical gland tuberculosis. Studies of the relative frequency of phthisis in people, breast and bottle fed, have led to similar conclusions. Speck, on his own observations and those of Jacob and Pannwitz, Schroeder, Servaes and others, concluded that 73 % of consumptives were breast fed, and 27 % were bottle fed.

Oberland studied the conditions of human beings and cattle in respect of tuberculosis in 97 Norwegian farms, and it seemed there was some kind of relation, but in what direction was not clear. Of 522 animals on farms in which there were tuberculous human beings, 6·7 reacted to tuberculin, whereas in 635 animals on farms in which

the human beings presumably were free from tuberculosis only 2·5 % reacted. In Denmark, Rördam believes that there is no perceptible relation between human and bovine tuberculosis as far as can be elicited by epidemiological studies. As I have already pointed out, the factors in such countries are so complex and difficult of isolation that a difference of opinion is not to be wondered at. There are, however, clear evidences from countries in which the problem of bovine tuberculosis is simpler in as much as milk is not a staple article of diet or is not used at all. In such instances the general result shows that tuberculosis in all its forms may be prevalent in man to an extent equal to or greater than that in the more civilized countries which have been the main objects of study in the past, and in which the conditions are admittedly of a highly complex character.

Japan. The facts with relation to this country were first made widely known by Heymann, who based his conclusions on the evidence of Miyake, surgeon in Thokoshima, Tade, the gynæcologist and pediater in Nagoya, and the medical historian Shishido in Aïchen, who has made a special study of the milk problem in Japan. Aoyama, Shiga, and particular Kitasato, have subsequently added to our knowledge. The main conclusions reached are that—(1) Human tuberculosis in almost all its forms is as widely spread in Japan as in other countries. (2) Intestinal tuberculosis is not uncommon, although sucklings are fed on the milk of the mother or a nurse in almost all cases (99% Shiga). (3) There are large areas in which the cattle are entirely free of tubercle, in spite of the frequent occurrence of tubercle among the inhabitants. The indigenous cattle are under natural conditions almost insusceptible to perlsucht, whereas imported animals and crosses are.

With regard to the use of milk, Shishido relates that 2,000 years ago the use of milk as an article of diet in Japan was unknown. Later, there are references that it was used. The civil war, which lasted from the beginning of the 14th century and ended with the triumph of the Tokugawa dynasty in 1686, destroyed to a large extent the culture of Japan, and developed in a higher degree the doctrines of Buddha with its vegetarian enforcements. At any rate, evidence shows that milk ceased to be an article of diet. To a certain extent the fact that the cattle were mainly used for draft purposes and were incapable of secreting milk in large quantities, contributed to this. Up till 40 years ago milk and milk preparations were not used as articles of diet. The first dairy was opened in Yokohama in 1863, and was regarded as a curiosity. After Mutsohito ascended the throne (1867) and western civilisation began to permeate the Japanese empire, the conditions of life began to be changed, and milk was consumed, especially by the well-to-do, among whom it has largely remained. Among the masses cow's milk has found no recommendation. Apart from its price the Japanese mothers have set a high value on human milk. A proverb

says, "One sho (1·8 litres) mother's milk is worth 3770 measures of linen, 23,000 bundles of rice straw, and more than 10,850 bushels of rice." As illustrating the small quantity of milk used in Japan, Kitasato, on the basis that a milch cow in Japan yields only 5 litres of milk a day, calculates the amount of milk consumed per head per diem is 2·825 c.c.

The problem of tuberculosis in Japan is of still greater interest in that the native races of cattle are free from the disease, whereas imported cattle and crosses are extensively affected. Thus Kitasato cites instances in the Mikata and Asako districts of Jasima in Hujago-Ken, where the human beings suffer from tubercle, although the cattle which are indigenous do not.

YEAR.	Inhabitants.	Total Deaths.	Deaths from Tuberculosis.	Number of Cattle.	Deaths in Cattle.	Bovine Tuberculosis.
1898 ...	78,383	1,633	92	7,353	58	—
1899 ...	78,474	1,509	111	7,822	140	—
1900 ...	79,167	1,451	84	7,748	95	—
1901 ...	79,619	1,343	87	7,687	104	—
1902 ...	80,650	1,446	100	7,354	68	—
	396,293	7,382	474	37,964	465	—

The number of deaths from tuberculosis is 6·4 % of the total deaths.

With regard to the frequence of human tuberculosis in Japan, in comparison with other countries, the following figures are of interest.

Deaths from phthisis per million living:—

Japan ... ... 1891–1895 = 1,354.
England ... 1894–1897 = 1,358.
Germany ... 1894–1897 = 2,245.

Mortality from phthisis per million living between 15 and 60 years of age:—

Japan ... ... 1891–1895 = 1,658.
England ... 1893–1895 = 2,075 (15–65 years).
Germany ... 1895–1896 = 2,947.

Mortality from phthisis per 10,000 deaths at ages 15–60:—

Japan... ... 1899 = 1,955.
England ... 1893–95 = 2,158 (15–65 years).

Considering, as we have seen that the Japanese suckling is reared on the breast, one would expect that the tuberculosis would be very much less than in European countries. The clinicians in Japan report to the contrary. The statistics confirm their observations. Of 1,000 living born children in Japan in 1899, 1·3 died in the first year from tuberculosis. Of a similar number born in Germany, 2·3 died in the same time.

The English statistics, which appear to show a higher figure, cannot be taken as altogether trustworthy, in so far that more than one writer has pointed out the tendency to diagnose many wasting diseases in children as tabes meseraica without sufficient justification. It may be pointed out that accurate official statistics have been published in Japan since 1875.

Turkey. In this country Rieder Pascha (1904) has drawn attention to the enormous dissemination of tuberculosis, although the children are almost exclusively breast fed. He considers that dissemination of the disease occurs from the total disregard of all hygienic measures in this semi-civilised country.

Rumania. Babes (1900) reports that tubercle is very widely disseminated in this country, reaching very unusual figures in the towns (*e.g.*, Bukharest 36·6 deaths per 10,000 living; in Jassy 41·6). Babes asserts that bovine tuberculosis may be discounted as a factor in the case of Rumania, as in most of the districts with much human tuberculosis there are no milch cows, and sucklings are not nourished with animal milk.

Egypt. von Becker, Goebel, Emil Gotschlich have all dealt with this problem, and are unanimous that cattle tuberculosis and dissemination of tubercle by cows' milk can be discounted. As is well known, there is a large admixture of races in the Delta and Nile Valley, including Copts, Bedouins, Arabs, Berbers, Syrians, Armenians, Jews, Albanians, Bulgarians, Greeks, Turks, and others. Among this motley crowd the Berbers in particular are affected.

Gold Coast. On the Gold Coast, Fisch, who was 20 years a missionary, reports that 12% of his patients had tubercle, especially of the lungs and glands. The children are fed on palm oil or on the breast. Cows' milk does not exist.

Asiatic Turkey. At Urfa, in Upper Mesopotamia, Christ (1905) saw a large number of cases of tuberculosis, although the children are breast fed. Milk in this region is never drunk raw.

Singapore. According to information I have received personally from a former colleague, Dr. George Finlayson, now Bacteriologist to the city of Singapore, tuberculosis is the formidable disease among the natives. Milk is, on account of its high price, almost

never consumed by them. Further the cattle, which are imported for food purposes, almost never present the lesions of perlsucht.

Philippine Islands. In these islands tuberculosis causes the most deaths. In Manila the mortality is 5 per 1000 living. Surgical tuberculoses occur in proportions equal to those met with in Europe and America. On the other hand, tubercle of cattle, swine and goats, is almost unknown. (Whitmore, 1909).

New Zealand. In this country human tuberculosis is comparatively rare. According to the reports of Gilruth, however, bovine tuberculosis is comparatively common. In Otago 1,500 cattle, chiefly dairy cows, were tested with tuberculin and 15 % reacted. In the Dunedin *abattoir* of 9,700 cattle slaughtered, 200 were condemned for tuberculosis, not considering those in which the lesions were so slight as not to render the flesh in any way dangerous.

Faroe Islands. These Islands have always been of great interest epidemiologically on account of their isolation. As is well known, they were the subject of very important observations on measles by Panum in 1843. At the time of his visit he reported tubercle to be rare. In recent years, Boeg, who practised there between 1879 and 1898, found that this is not so. The population in 1906 amounted to 16,349 souls. Boeg obtained information of all consumptives, deceased or still alive, during the period of his residence, through death certificates, church registers, medical reports and journeys among the Islands. There were 354 cases, 305 of which died while he was there. These 305 deaths represented 8 % of the total deaths or 11·8 per 10,000 living. According to Westergaard, the sucklings in the Faroe Islands are breast fed, and the mortality among them is small (6·3 per 100 living, in comparison with 9·6 per 100 and 13·3 per 100 in Norway and Denmark). Boeg also studied the dissemination of bovine tuberculosis by means of tuberculin and satisfied himself that the native cattle are free from tubercle and that bovine tubercle has been imported from without.

Greenland is also of great interest in connection with these problems in as much as there are no cattle there at all. All travellers, however, like Saugman, Nansen, Kiaer, Rördam, Haven, Meldorf, C. Lange, are unanimous in their expression that tuberculosis in its various forms is rampant. According to Nansen, the children are breast fed till the 3rd or 4th year. If the mother dies and a nurse cannot be found they are left outside or thrown into the sea. Kiaer (1900), long in practice in North Greenland, considered that 50 % of all individuals under 25 years showed symptoms of tuberculosis, a degree also estimated by Haven (1882). Tuberculous meningitis is one of the most frequent causes of death. Tuberculosis of bones is common, while scrofula and lupus are rare. Gustav Meldorf, in 1904, gives an account of the reports of all the

early Greenlandic physicians on the appearance of tuberculosis. As early as the colonisation of Greenland by the Dane Hans Egede in 1721, it seems to have been frequent. In the years 1897–1903, among 1,621 patients, Meldorf treated 50 cases of consumption. According to him, all forms of tuberculosis occur with relative frequence. Among the Loucheux Indians, and even among the half-breeds living in Northern Canada, within the Arctic circle, Laing records the prevalence of tuberculosis of the lungs, glands and testicle, but he had not seen tubercle of the bones and joints.

These reports are at variance with the statements of N. Raw, that pulmonary tuberculosis is essentially of human origin whereas most of the other forms are probably bovine.

III. Bacteriological evidence. The important bacteriological questions in connection with the subject of tuberculosis are:—

(1) Is it possible to distinguish human from bovine bacilli?

(2) Are the distinguishing features constant, or can the bacillus of one type become converted into those of another type?

(3) What is the relative frequence of these two types of bacilli in human tuberculous lesions?

With regard to the first of these problems, a definite answer can be given with reference to almost all the cultures which have been isolated. It is agreed on all sides that there are striking differences between the two types of bacilli, and while some maintain that these differences are relatively hard and fast, others consider that there are intermediate types often difficult to classify. The English Commission on Tuberculosis may be said to hold the latter view, although they also admitted great differences between individual races. It is perhaps unnecessary to consider in detail what these differences are. Suffice it to say that they are (1) morphological and cultural; (2) chemical; (3) the pathogenic effects.

The morphological and cultural characters have been extensively studied, especially by Th. Smith, Ravenel, Dorset, Wolbach and Ernst, Kossel, Weber and Heuss, and found to be fairly constant. Theobald Smith in particular separated a human or "sputum" type from the bovine type. It must be admitted, however, that others consider that the characters, like length, the difficulty of growth of the bovine type, the appearances of the growth, the alteration of the medium, are perhaps not so sharp as has been asserted by the above writers. This view is held especially by Arloing, Fibiger and Jensen, Lydia Rabinowitch, Beitzke, the English Commission and others. A good deal of difference of opinion has been expressed with regard to the changes in the medium brought about by the two

types. As is well known, Theobald Smith showed that in glycerine bouillon with a degree of acidity corresponding to 2 % normal acid (phenol phthalein indicator), bovine bacilli causes the acidity to diminish, and may even develope an alkaline reaction; whereas with human bacilli the acidity diminishes up to a point, but is regained more or less completely. While agreeing in the main with Smith's facts, the English Commission differed in its interpretation regarding the change as a gradual one and due to the intensity of the growth. Fibiger and Jensen distinguish three types of reaction.

Differences in pathogenic properties. As a rule, bovine bacilli are much more pathogenic for animals than human bacili. Great differences of opinion have existed, however, as to the degree of virulence; these differences being due to varying methods of experimentation, varying doses and varying interpretations put upon the results. In recent writings there has been a progressive tendency to standardise the experiments so as to make the work of different observers really comparable. With regard to cattle, a large number of tests have now been made, and it may be accepted as a fact that bacilli of human origin are for the most part much less pathogenic for cattle than bacilli of bovine origin. The study of a series of races of bacilli from man have demonstrated the undoubted existence of bacilli of bovine character. Such bacilli are rare, however, in comparison with those which are only slightly pathogenic for cattle. As the expense of experimenting with cattle is very great, it has been largely replaced by using the rabbit. It was pointed out that Villemin had noticed differences between human and bovine bacilli when this animal was used, likewise, Orth, Straus and others, especially Theobald Smith, Kossel, Weber and Heuss, Heymanns Oehlecker. The introduction of known quantities of bovine and human bacilli into rabbits yield more or less constant results. Thus, ·001 grm. of bovine type interavenously kills rabbits in about three weeks, whereas ·001 grm. of culture of human type produces no symptoms in this period, but perhaps later shows a chronic tuberculosis. ·01 grm. bovine type subcutaneously kills in a relatively short time, the same dose of human type producing, for the most part, only a local tuberculous abscess.

Bacilli obtained from sputum or lesions of consumption. Two classes of experiments have been made, viz., by ingestion of sputum, and by isolation of pure cultures with subsequent inoculation of such cultures intravenously or subcutaneously. The results of the latter kind of experiments are unequivocal. Bacilli from sputum of human pulmonary tuberculosis are, one may say without exception, of the typus humanus. This statement is based on the published work of Theobald Smith, Vagedes, the German Commission, the English Commission, Gorter, and especially the large series published by Dieterlen (50 cases), Kitasato (152 cases), Park (290 cases). In association with my assistant, Mr. Paul Fildes, I have tested 23

strains of bacilli, isolated either by ourselves or by Dr. Radcliffe at the King Edward VII. Sanatorium. In no instance did we produce other than a local suppurative effect, although the rabbits were kept alive for periods up to four months. So far as I can learn from medical literature, 602 strains of tubercle bacilli have been isolated from sputum or lung, and, with only one exception, all were proved to be of human type.* The exception is that published by Stuurmann. It was a peasant girl, aged 27, whose sputum contained many T.B. The sputum was inoculated into a guincapig, and cultures were obtained from this animal. The cultures inoculated intravenously into a healthy bull calf six weeks old, caused death in three weeks with generalised tuberculosis. Two other calves also succumbed. The examination of the sputum was made on only one occasion, and it is to be regretted that no attempts were made to determine whether the infection was a mixed one or a pure bovine one.

Constancy of types. Although human tuberculous sputum contains bacilli of human type only, it might be urged that bovine bacilli after entry to the human body might develope human characters. Indeed, we know that Behring asserts that the milk is the main vehicle in which the virus of consumption is conveyed. The constancy of type, therefore, becomes a very important question, and, as is usually the case, there is some difference of opinion on the subject. Arloing, for example, considers that it is possible to obliterate the differences existing between human and bovine bacilli, which he holds to be practically identical. The balance of opinion, however, is in favour of the stability of the two types. The English Commission on tuberculosis is generally credited with the demonstration of instability of the bacillary types. In a recent paper by Cobbett (*J. of Path. and Bact.*, 1910, xiv., p. 563), one of the workers for the Commission, I find it stated that these experiments "were done without the special precautions as to isolation, which subsequent experience showed to be necessary in passage experiments." A repetition of the experiments showed no modification whatever of the human type on passage through calves. Cobbett says, with regard to the early experiments, "I do not myself think they lend any real support to this theory (of instability), and I think it is only fair to myself to state that my earlier series of experiments were published without my comments, and my later experiments, which had negative results, were reserved for future publication."

We have thus arrived at more or less unanimity. Practically every strain of bacilli isolated from human consumption is of the typus humanus. There are no conclusive experiments which demonstrate the conversion of typus bovinus into typus humanus.

* Since the above was written, Möllers has published an additional list of 51 cases of phthisis, all yielding bacilli of the human type, and bringing the total up to 653.

It is interesting to add that the very exact experiments on ingestion and inhalation carried out in Flügge's laboratory by Findel, Reichenbach and Alexander, all show the enormously greater susceptibility of animals to inhalation as compared to ingestion.

In conclusion, it would appear justifiable to draw the following conclusions from these data :—

(1) Pulmonary tuberculosis is produced almost, if not exclusively, by bacilli of the *typus humanus*.

(2) Pulmonary tuberculosis is essentially an inhalation disease.

(3) Previous methods of prophylaxis as regards tuberculous sputum should be enforced with even greater vigour.

(4) Bovine tubercule bacilli play a relatively unimportant rôle in the production of tuberculosis in man.

Although no one can doubt that tuberculosis is an infective disease, it is very difficult to determine the exact degree of infectivity. To a certain extent this is due to our inability to diagnose the disease in its very early stages, and to the fact that there must be a considerable degree of resistance, inasmuch as a large number of individuals show that they have partially or wholly recovered from the infection, as demonstrated by the existance of healed and latent lesions. We are thus brought face to face with a further aspect of this problem, viz., the soil on which the bacillus flourishes, and it would seem illogical to consider the whole problem of tubercle as merely one of infection. Indeed, it is probable that the doctrine of a tuberculous diathesis or predisposition has been neglected too much. This aspect of the subject has been considered in great detail by Pope and Pearson, who have come to the conclusion, on a wide series of statisties, that the diathesis must be made to assume a much greater importance that has been done for some time past.

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